Trend Watch

STRATTERA: Ups, Downs, and Emerging Uses

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ABSTRACT: Although overall prescribing of atomoxetine hydrochloride (HCl) (Strattera) continues to decline, recent anecdotal reports suggest emerging uses of the product in combination therapy. In this article we examine trends in atomoxetine (HCl) prescribing as well as use in combination with other psychotropic classes. An expert commentary is provided on the data.

KEY WORDS: ADHD, attention deficit hyperactivity disorder, pharmacology, atomoxetine hydrochloride, Strattera, augmentation

Following introduction to the US market, use of atomoxetine hydrochloride (ATX) (Strattera®) soared to its peak in late 2004. Since that time, use of the product has been in steady decline possibly because the product is perceived to have lower efficacy on hyperactivity/behavioral issues. Although overall prescribing of ATX continues to decline, recent anecdotal reports suggest emerging uses of the product in combination therapy. In this article we examine trends in ATX prescribing as well as use in combination with other psychotropic classes.

METHODS

We obtained data from two different sources: 1) quarterly total retail prescriptions of ADHD therapies, including ATX from Vector One National (VONA), which captures nearly half of all prescription activity in the US, and 2) annual data from Verispan's Prescription Drug and Diagnosis Audit (PDDA) database regarding concomitant therapy. PDDA captures data on disease states and associated therapy from 3,100 office-based physicians representing 29 specialties across the US.

RESULTS

As seen in Figure 1, share of ATX rose to a peak of 17.3 percent in the quarter ending September, 2004, approximately two years post-introduction to the US market. Since that time, the product has been in a steady decline with current share of total prescriptions at 9.8 percent by the quarter ending December, 2006. Although prescribing of ATX has continued to decline, it appears that combination use of the product is increasing. Comparing 2005 to 2006 suggests that use of ATX in combination with other psychotropics has increased from 19 percent to 29 percent. The three classes of agents most commonly used in combination with ATX increased over the past year as follows:

- Stimulants: 11% to 18%
- Atypical antipsychotics: 1% to 7%
- Antidepressants: 4% to 6%.

EXPERT COMMENTARY—Prescribing Trends for Strattera

by David Feifel, MD, PhD

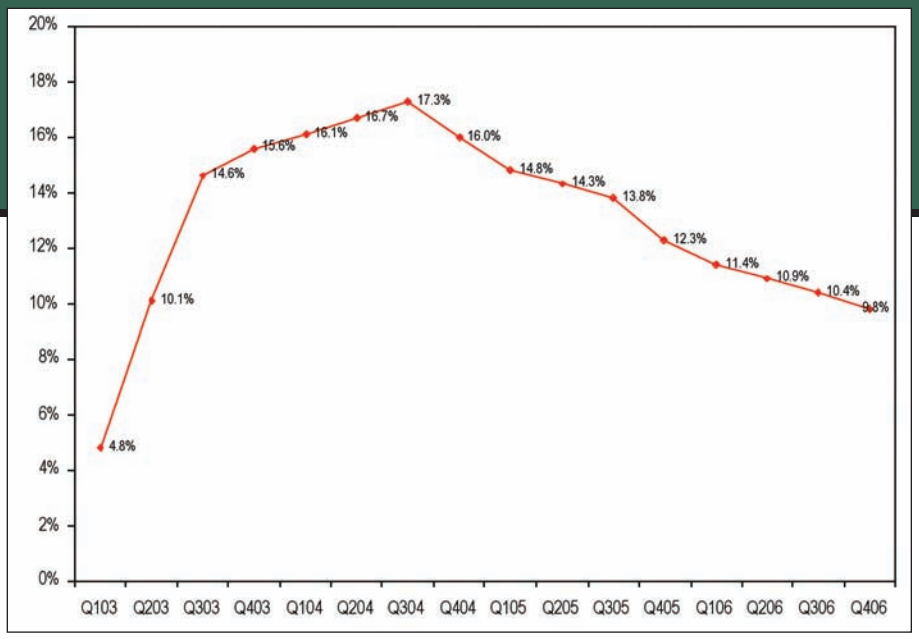

FIGURE 1. Quarterly share of atomoxetine HCl among ADHD therapies. Source: Verispan VONA, Quarter March 2003 – Quarter December 2006.

As the Trend Watch analysis indicates, the pattern of use for atomoxetine (ATX) has not reflected the conservative growth pattern typically seen with a newly approved drug. I believe the initial remarkable growth of ATX represented in its first 18 months on the market was due to both a strong perceived need for a nonstimulant alternative for treatment of ADHD and the high expectations regarding what ATX could deliver therapeutically.

ATX is a first-in-class, nonstimulant, FDA-approved treatment for ADHD. It is also the first agent of any kind to be FDA-approved for ADHD in adults as well as in children and adolescents. Because of widespread apprehension on the part of many parents, adult ADHD patients, and physicians about the use of stimulants and because of the practical barriers associated with prescribing a controlled, schedule II medication (e.g., restrictions on refills, special prescription forms), there was a very receptive pre-existing market for an approved ADHD treatment not classified as a controlled drug by the FDA. As such a drug, ATX obviated concerns about drug abuse that has stigmatized stimulants, and it negated the complexities of prescribing stimulant drugs, which are categorized as Schedule II by the FDA. Furthermore, the expectation of what ATX could deliver to patients was set unrealistically high when it initially entered the marketplace. Phase III clinical studies had demonstrated robust statistical advantages for ATX compared to placebo that began as early as one week.[1] Using this data to aggressively market ATX at its launch, pharmaceutical representatives seemed to have fostered a notion among clinicians that ATX was as efficacious and fast in onset as stimulants—medications with established high response rates and rapid-onset of effect. In the absence of their own experience with the medication or head-to-head studies comparing the drug to stimulants, this claim understandably seemed credible to many clinicians, and this contributed significantly, in my opinion, to the rapid rise in ATX use soon after if was launched.

The decline in use that ATX has undergone after peaking in 2004 mostly reflects, in my opinion, a gap in the high expectations established around the time of launch and the actual experience of clinicians who have used ATX. Many patients and prescribers have come to feel that ATX does not exhibit therapeutic parity with stimulants. Indeed, it is now widely accepted that the therapeutic effects of ATX accrue more slowly than the immediate-onset benefits experienced by most patients using stimulants, which is consistent with the premarketing studies of ATX. Although they often show a statistical advantage for ATX versus placebo at early measurement points (e.g., at 1 week in some studies), these studies also always demonstrate that this advantage grows in magnitude over subsequent weeks.[1] The important point in this regard is that statistical separation from placebo in a clinical trial does not necessary translate into clinically meaningful therapeutic effects, and the early separation of ATX from placebo, which was statistically significant, does not typically reach a clinically meaningful threshold in most patients until several weeks of exposure to the drug. Furthermore, it is now also widely believed that the response rate produced by ATX is lower than that of stimulants. This point has been demonstrated in several head-to-head comparisons of ATX and stimulants, including one using a long-acting formulation of methylphenidate conducted by the manufacturer of ATX, Eli Lilly (unpublished data).

So should the decline in ATX use be interpreted as an indication that this compound is not a "player" among the line-up of existing ADHD medications and is destined to be a psychotropic bench-warmer? I do not think this is case by any means. Rather, I think the decline in ATX prescriptions since 2004 most likely represents a realignment of inflated expectations with the medications' realities, much like the correction the US is now seeing in housing sales, which had become unsustainably inflated by low interest rates. The large and scientifically credible body of data demonstrating that ATX is efficacious for ADHD is irrefutable in my opinion. In addition, there is emerging evidence that among ADHD patients who respond to ATX, this drug may provide therapeutic

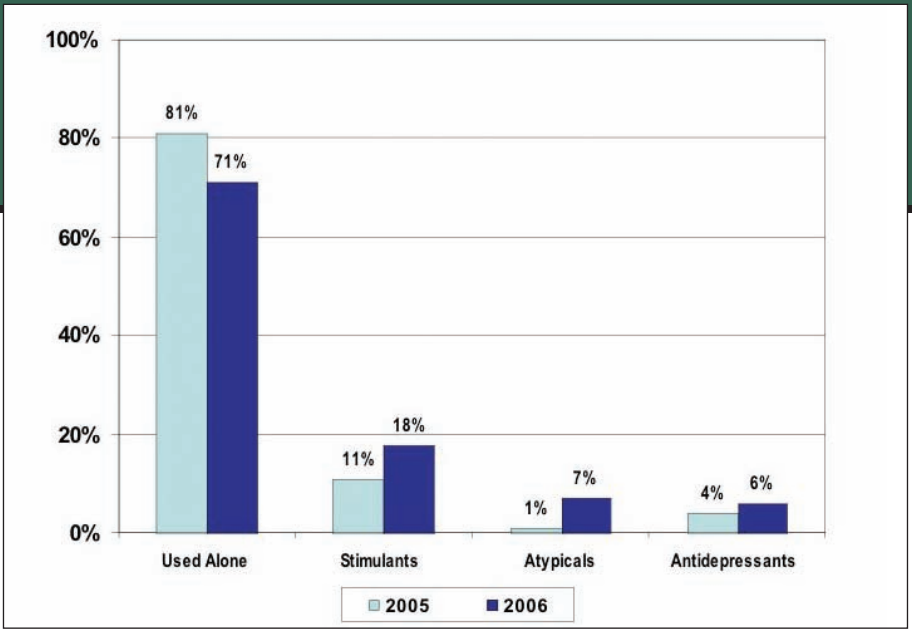

FIGURE 2. Use of atomoxetine HCl alone and in combination with other classes. Source: Verispan PDDA, Concomitant Class for atomoxetine HCl 2005 and 2006.

advantages over stimulants that offset its relatively longer time to onset of action. These potential advantages, in addition to the freedom from stimulant prescription restrictions already discussed, include continuous symptom relief that is not anchored by the time of ingestion, compared to the time-limited relief (typically 4–12 hours) that characterizes stimulant formulations and makes timing of their ingestion an important consideration for patients.[2] Also, there is evidence that when a patient responds to ATX, the therapeutic effects do not rapidly dissipate with discontinuation of the drug, as is the typical case with stimulants. Thus ATX may be more forgiving of missed doses than stimulants.[3]

However, to achieve optimal benefits of ATX, many clinicians will need to readjust how they utilize this compound. This will include needing knowledge about optimal patient selection, optimal trial duration, how to educate and prepare patients for treatment with ATX (especially those previously treated with stimulants), and how to most effectively measure efficacy, which requires more detailed assessment of target ADHD symptoms (e.g., using rating scales) owing to fact that ATX's benefits are much more insidious and far less dramatic in onset compared to stimulants, making it easy for patients on ATX to underestimate their clinical improvement.

The Trend Watch data also illustrate another very interesting phenomenon that may ultimately reflect the most important and effective use of ATX. This phenomenon is the trend toward less use of ATX as a monotherapy and greater use of it in combination with other psychotropics. The most frequent combination use of this kind, according to the Trend Watch data, is ATX concurrent with stimulant medication, a practice that seems to have increased by nearly 65 percent in 2006 compared to 2005 (18% vs. 11%). Another area that appears to be undergoing rapid growth is the concurrent use of antipsychotics and ATX, which increased seven-fold in 2006 compared to 2005. I suspect the latter combination is used primarily in children with ADHD and related behavioral problems, since atypical antipsychotics are now widely used to treat that population.[4]

Interestingly, this shift in use of ATX from monotherapy toward adjunctive therapy is purely a bottom-up or "grass-roots" phenomenon, driven by pharmacologically progressive clinicians, since there is virtually no rigorous research data to inform this practice. While stimulants, the most frequently prescribed medication for ADHD, are generally highly effective, they do not induce a full-remission of symptoms. Furthermore, some patients do not tolerate the optimally therapeutic dose of stimulants. The opportunity to safely add another proven ADHD medication to enhance the therapeutic outcome is an important potential opportunity to provide better treatment for this population. ATX's distinct pharmacological mechanism, selective and potent noradrenergic reuptake inhibition, relative to that of stimulants and that of antipsychotics, makes combination of ATX with these other psychotropics a pharmacologically rational practice, in theory at least, for difficult to treat ADHD and ADHD with comorbid behavioral disorders— just as combination of thiazide-diuretics, beta-blockers, and ACE-inhibitors can be effectively combined to provide superior control of difficult hypertension compared to monotherapy, because each of those class of drugs reduces blood pressure by a distinct mechanism. What is now urgently needed going forward are well-controlled studies investigating the safety and therapeutic benefits of combination regimens, such as ATX-stimulant and ATX-antipsychotic, in order to inform these emerging practices.

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